

REMARKS

Claims 27-34 are pending.

Applicants respectfully traverse the present rejections.

35 U.S.C. § 101

Claims 27-34 remain rejected under 35 U.S.C. §101 as allegedly not supported by either an asserted utility that is specific and substantial or by a well-established utility. The Office action maintains that the remaining issue "is not whether the expression levels based upon DNA were significantly different in the tested tumors, but rather whether this data makes it more likely than not that the protein encoded by the gene is overexpressed." Page 3 of the Office action mailed 7/10/08.

US Patent No. 7,208,308 as evidence of utility:

Applicants respectfully maintain that issued US Patent No. 7,208,308 (the "'308 patent") is persuasive evidence that the gene amplification of PRO347 provides a specific and substantial utility for the claimed polypeptide. The Office action maintains that "each application is examined on its own merits. . . [and a] review of the '308 patent does not indicate a clear reason for allowance." Page 3 of the Office action mailed 7/10/08. Allegedly, the final rejection during prosecution of the '308 patent "may have been withdrawn based on a determination that the polypeptide was a serine protease rather than for any reason related to the gene amplification data in the specification." *Id.*

Applicants respectfully disagree. The prosecution history of the '308 patent demonstrates that Genentech, Inc., assignee of both the present application and the '308 patent, asserted and relied on utility based on gene amplification. In particular, Example 92 asserts:

This example shows that certain PRO polypeptide-encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers

such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers.

Before being allowed, the claims in the '308 patent were rejected for alleged lack of utility.

In response to that rejection, the Applicant of the '308 patent stated:

Applicants have asserted utility for the instantly claimed PRO343 polypeptide based on amplification of the PRO343 gene in the 'gene amplification assay' described in the instant specification in Example 92.

See page 4 at Tab A, Amendment and Response filed 11/9/05. Indeed, the Notice of Allowability for the '308 patent reports that the '308 patent was allowed in response to the amendment filed August 15, 2006. See Tab B, Notice of Allowability. That August 15, 2006 Amendment was the Applicants' submission of the declaration of Randy Scott, Ph.D. See Tab C, Amendment and Response dated 8/15/06. (Applicants submitted the same declaration of Randy Scott in the present application on December 7, 2006). In his declaration, Dr. Scott testifies about the utility of DNA microarrays. Example 92 of the '308 patent uses microarray technology to identify amplified genes. Dr. Scott also testified that in his experience, which includes more than 15 years of personal experience with DNA microarray techniques, gene amplification more likely than not correlates with overexpression of mRNA and ultimately with polypeptide overexpression. See Tab C, Declaration of Randy Scott, Ph.D. Thus, the '308 patent was issued because the PTO found gene amplification more likely than not correlated with mRNA and polypeptide overexpression. Applicants respectfully maintain that issuance of the '308 patent is persuasive evidence that the present claims are supported by a specific, substantial, and adequate utility.

Genentech Patents Including Microarray Data as Evidence of Utility:

Applicants respectfully disagree with Office action's rejection of issuance of at least 16 patents identified in Applicants' responses filed February 25, 2008 and August 17, 2007 as evidence of utility in the present case. Applicants maintain issuance of these patents, where the asserted utility is similar to that relied on by Applicants in the present case, presents persuasive evidence that one of ordinary skill in the art would, more likely than

not, accept Applicants' assertion of utility based on gene amplification of PRO347 as disclosed in Example 28 of the present application.

For example, as previously discussed the claims of US Patent No. 7,276,577 (the "'577 patent") are similar to the claims pending herein. The '577 patent issued when the Board of Patent Appeals and Interferences found that the '577 patent claims were supported by an adequate utility because "[a]s demonstrated by the Polakis and Smith Declarations . . . there is a strong correlation between mRNA levels and protein expression. . . [and thus] [t]he use of PRO1866 polypeptide as a cancer marker is sufficient to demonstrate utility." See Tab D, Decision of the USPTO Board of Patent Appeals and Interferences, Appeal No. 2006-1469 at pages 9-10. Applicants assert this same specific and substantial utility for the claimed PRO347 polypeptides at paragraph 703 of the present application:

[0703] This example shows that the PRO327-, PRO344-, PRO347- PRO357-, and PRO715-encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers. . . . **These amplifications also are useful as diagnostic markers for the presence of a specific type of tumor type.**

Emphasis added.

The Office action rejects this similarity because allegedly the cases cited by Applicants presented microarray data of mRNA whereas the present application provides data of amplified genomic DNA. Although the data may be different, Applicants respectfully maintain that allowance of these 16 patents presents persuasive evidence that the PTO acknowledges it is more likely than not that overexpression of mRNA correlates with overexpression of the polypeptide.

Gene amplification data of Example 28 as evidence of utility:

As in the above-discussed patents, Applicants have asserted utility for the instantly

claimed PRO347 polypeptide based on amplification of the PRO347 gene in the "gene amplification assay" described in the instant specification in Example 28.

The Office action states that the significance of the data set forth in Example 28 may be questioned based on the alleged "absence of factual support for the [Dr. Goddard's] opinion [that gene amplifications of 2-fold or more are considered significant]." Page 5 of the Office action mailed 7/10/08. Specifically, the Office action notes that "the facts are that while 9 colon tumors showed increased gene amplification, 8 colon tumors did not. Furthermore, the control used in the instant application was not a matched non-tumor sample but rather was a pooled DNA sample from healthy subjects." *Id.*

Applicants respectfully disagree that there is an absence of factual support for Dr. Goddard's Declaration and that the facts identified by the Office action make it more likely than not that one of ordinary skill in the art would not accept Applicants' asserted utility. Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 28 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 10, including primary lung and colon cancers of the type and stage indicated in Table 9. Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 10. As explained at paragraph 0705, the results of TaqMan™ PCR are reported in ΔC_t units. One unit corresponds to one PCR cycle of approximately a 2-fold amplification, relative to control, two units corresponds to 4-fold amplification, 3 units correspond to 8-fold amplification, etc. PRO347 showed ΔC_t values of approximately 1.01 -2.73 in thirteen lung tumors and 1.1.01-2.1 in nine colon tumors. Thus, Example 28 demonstrates gene amplification of at least 2.00-8.00 fold amplification in 22 lung and colon tumor samples.

In support of the showing that the gene amplification values for PRO347 DNA are significant in lung or colon cancer, Applicants submitted, with their Response mailed June 24, 2003, the Declaration of Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold in a tumor sample relative to a normal

sample by the gene amplification assay discussed at pages 119-137 of the present application, is useful as a marker for the diagnosis of cancer:

[a]n at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number . . . as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Goddard Declaration, paragraph 7 (emphases added). In her declaration, Dr. Goddard explains that the TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression:

Amplification of protooncogenes has been studied in a variety of human tumors, and is widely considered as having etiological, diagnostic and prognostic significance. This use of the quantitative TaqMan PCR assay is exemplified by the following scientific publications: Pennica *et al.*, Proc. Natl. Acad. Sci. USA 95(25):14717-14722 (1998) (Exhibit E); Pitti *et al.*, Nature 396(6712):699-703 (1998) (Exhibit F) and Bieche *et al.*, Int. J. Cancer 78:661-666 (1998) (Exhibit G).

Goddard Declaration, paragraph 6.

Although supported by the Goddard Declaration, the Office action alleges that the data in Example 28 is not sufficient to demonstrate gene amplification in lung or colon tumors. Applicants respectfully disagree. For utility, PRO347 does not have to be amplified in every incidence of colon cancer. Indeed, there is no requirement that the claimed PRO347 polypeptide identify all types and cases of colon cancer. Rather, the utility standard only requires that the asserted utility be more likely than not. The data reported at Table 9 reports that PRO347 was amplified in 9 of the 17 colon tumors tested. Thus, amplification of PRO347 more likely than not is useful as a marker for the diagnosis of cancer. Indeed, Applicants note that the claims are not limited colon tissue but rather are directed to colon and lung tissue. The data reported at Table 9 reports that PRO347 was amplified in 13 of the 15 lung tumors tested. Thus, within the scope

of the claim it is clear that amplification of PRO347 more likely than not is useful as a marker for the diagnosis of cancer. The Office action however, rejects this data because it demonstrates gene amplification while the claims are to polypeptides. According to the Office action, the art teaches that a correlation between gene amplification and polypeptide overexpression cannot be presumed. Applicants respectfully disagree.

Orntoft, Pollack, Hyman, and the Scott and Polakis Declarations as evidence of utility:

Orntoft *et al.* studies transcript levels of 5600 genes in malignant bladder cancers, many of which were linked the gain or loss of chromosomal material, and found that in general (18/23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Orntoft *et al.* also showed a clear correlation between mRNA and protein expression levels, stating that "[i]n general there was a highly significant correlation ($p < 0.005$) between mRNA and protein alteration . . . 26 well focused protein whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p < 0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2, to page 44, column 2). Accordingly, Orntoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

However, the Office action rejects Applicants' reliance on Orntoft because allegedly Orntoft looked at "regions of chromosomes with clusters of chromosomal material containing strong gains." Page 8 of the Office action. Additionally, the Office action asserts that "[i]f PRO347 is not part of a cluster showing strong gains, then the findings of Orntoft are not applicable." *Id.* Applicants respectfully disagree. Applicants rely on Orntoft for the teaching that in general gene amplification correlates with polypeptide overexpression. Orntoft clearly teaches this correlation as discussed above. Moreover, when Orntoft is considered with the other references relied on by Applicants, it is clear that correlation between gene amplification and protein overexpression is more likely than not.

Similarly Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. The Office action, however, alleges that “[s]ince Hyman *et al.* found that less than half of the amplified genes were overexpressed at the mRNA level” Hyman supports the Office’s position. Page 9 of the Office action mailed 7/10/08. Applicants respectfully disagree. Hyman reports that “[t]hroughout the genome, both high- and low-level copy number changes had a substantial impact on gene expression, with 44% of the highly amplified genes showing overexpression.” Abstract. Hyman concludes that the disclosed analysis provided: “(a) evidence of a prominent global influence of copy number changes on gene expression levels; (b) a high-resolution map of 24 independent amplicons in breast cancer; and (c) identification of a set of 270 genes, the overexpression of which was statistically attributable to gene amplification.” Page 5. Hence, Hyman teaches gene amplification correlates with protein overexpression.

In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 33 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellant’s position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

The Office action points out that Pollack does not address protein expression levels but as stated above at page 6, the PTO clearly accepts that increased mRNA levels correlate with protein overexpression levels. Further, as previously argued, the above cited references and the correlation between mRNA and protein levels are further supported by the Declaration of Randy Scott, Ph.D. They are also supported by the First and Second Declarations of Dr. Polakis, which were submitted November 21, 2005 and June 20, 2006. Dr. Polakis is the principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. Dr. Polakis’s declaration further evidence that in general, mRNA expression correlates well with protein levels. As Dr. Polakis explains, the primary focus of the microarray project was

to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the projected extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states, that for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increase mRNA levels are predictive of corresponding increased levels of the encoded protein."

Godbout, Li, Konopka and Pennica do not outweigh the above-discussed evidence:

The Office action relies on references by Godbout, Li, Konopka and Pennica as evidence against the above-discussed evidence relied on by Applicants. Applicants respectfully submit that the teachings of Godbout, Li, Konopka, and Pennica do not outweigh the evidence relied on by Applicants.

Specifically, the Office action alleges Godbout teaches co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell. However, PRO347 is not a co-amplified gene as demonstrated by epicenter mapping. Godbout does not teach that gene amplification fails to correlate with mRNA expression or polypeptide expression outside of the context of a gene being co-amplified or conferring selective advantage. Thus, Godbout does not provide evidence against Applicants' asserted utility.

Similarly, Li teaches that "genes that are concurrently amplified because of their location with respect to amplicons" generally do not show correlation between gene amplification and mRNA or polypeptide overexpression. However, just as Godbout is not persuasive evidence, Applicants respectfully disagree that Li is persuasive evidence in the context of the present invention. Framework and epicenter mapping analyses were carried out for PRO347 to confirm that PRO347, and not some other gene, is responsible for the observed gene amplification. This coupled with the high rates of observed amplification (approximately 2 to 8 fold amplification in nearly 70% of all tissues tested) indicates that PRO347 gene amplification more likely than not correlates with overexpression of the PRO347 polypeptide.

As explained above, the patentee of US Patent No. 7,208,308, Genentech, Inc, who is the assignee of the present case, asserted a diagnostic utility for the polypeptide claimed in the '308 patent based on gene amplification resulting in overexpression of the mRNA and subsequently, the protein of the gene. The examiner in that case repeatedly rejected but ultimately accepted that assertion of utility. In rejecting the assertion of utility, the examiner relied on two references relied on in the present case, Pennica and Konopka. Ultimately these references were overcome because the combined teachings of Pennica *et al* and Konopka *et al* were not directed towards the claimed PRO343, nor towards genes in general but rather are to a single gene or genes within a single family. Thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. For these same reasons, Pennica and Konopka do not support the present rejection of the claims pending in this application and are overcome.

Indeed, Applicants respectfully disagree that the teachings of Pennica demonstrate that more likely than not one of ordinary skill in the art would not expect gene amplification levels to correlate with protein overexpression. First, *WISP-1* gene amplification and RNA expression levels examined in Pennica showed a significant positive correlation. Second, although Pennica stated that *WISP-3* was not significantly amplified, it was amplified ($P=1.666$) and overexpressed. Third, although *WISP-2* gene amplification and RNA expression levels seemed to be inversely related, Pennica suggests that this result might be inaccurate: "[b]ecause the center of the 20q13 amplicon has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." See Pennica at 14722. Thus, because the RNA expression pattern of *WISP-2* cannot be accurately attributed to gene amplification of *WISP-2*, this result should be disregarded. Indeed, the teachings of Godbout taken with Pennica suggest that Pennica's conclusion that the observed amplification is not actually attributable to *WISP-2* is correct. Moreover, as discussed above, in the present case, appropriate controls for aneuploidy were used and page 137 of the present specification explains the procedures performed to confirm that the observed gene amplification was attributable in the present case to PRO347. Therefore, for this additional reason, Pennica *et al.* does not make it more likely than not that the present invention is not supported by a specific, substantial, and credible utility.

For the reasons discussed above, Applicants respectfully maintain that the *totality* of this evidence currently under consideration demonstrates that it is more likely than not that PRO347 is overexpressed in lung or colon tumor tissues. For these reasons, Applicants maintain that this rejection is improper and request that it be withdrawn.

35 U.S.C. § 112 ¶ 1, Enablement-Utility

Claims 27-34 stand rejected under 35 U.S.C. § 112 ¶1, because it is alleged that the presently claimed invention is not supported by a substantial utility, and therefore, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, Applicants respectfully submit that the claimed polypeptide is supported

by a substantial utility. Thus, Applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

SUMMARY

Applicants believe that currently pending Claims 27-34 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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